

Differential Diagnosis of Metabolic Acidosis

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Without enough time to take that first sip of morning coffee, the paramedics roll in with an ill-appearing young adult female who has been vomiting for the last several hours. She is febrile and tachypneic. Her parents state that she has been depressed lately and even contemplated suicide, but seemed to be well at dinner the previous evening. Her initial lab results reveal an anion gap acidosis with a respiratory alkalosis, confirming your diagnostic suspicions. As you turn to discuss the findings with her family, the intern is tugging at your opposite sleeve worriedly reporting, “The patient we thought was suffering from alcoholic ketoacidosis doesn’t have any ketones in his urine.” As you take a breath to begin your explanation regarding the lack of ketones, a colleague at the clinic calls hoping to transfer a hypertensive, diabetic patient whom he believes has become severely hyponatremic and hyperkalemic secondary to renal tubular acidosis (RTA) syndrome. Desperately trying to recall the differences between RTAs, you find yourself wading through the MUDPILES of metabolic acidosis and HARDUP for answers from your inquisitive intern. Relax, go back to that full coffee, and read on....

Metabolic acidosis is defined as an acidemia created by primary increase in H^+ concentration or reduction in HCO_3^- concentration. Acutely, medullary chemoreceptors compensate for a metabolic acidosis by means of a hyperventilatory response, resulting in a reduction of $PaCO_2$, in attempt to increase the pH to normal. In an isolated metabolic acidosis, the degree of acute respiratory compensation can be predicted based on the following relationship: $PaCO_2 = (1.5 \times [HCO_3^-]) + 8$ (ie, the $PaCO_2$ is expected to decrease 1.5 mmHg for each mmol/L decrease in $[HCO_3^-]$). Chronically, the pH imbalance of a metabolic acidosis is opposed by increased renal reabsorption of HCO_3^- .

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Metabolic acidosis is created by one of three mechanisms: increased production of acids, decreased excretion of acids, or loss of alkali. Clinically, metabolic acidoses are divided into processes resulting in an elevated anion gap and a normal anion gap. The diagnosis and classification of metabolic disturbances are based on nearly simultaneous arterial blood gas and electrolyte panel measurements. Confirm internal consistency of the results by comparing the measured $[\text{HCO}_3^-]$ (reported with the electrolyte panel) and the arterial blood gas $[\text{HCO}_3^-]$ calculated by the Henderson-Hasselbach equation. These values should agree within 2 mmol/L. A pH of less than 7.35 without an increase in the patient's baseline PaCO_2 indicates the presence of a metabolic acidosis. Using the electrolyte panel, calculate the anion gap: $([\text{Na}] - [\text{Cl}] - [\text{HCO}_3])$. A normal anion gap is considered to be 8 plus or minus 4 mmol/L, making the hallmark of an elevated anion gap acidosis an anion gap of greater than 12. The anion gap represents unmeasured plasma anions. Elevation of the anion gap may be caused by a decrease in unmeasured cations (eg, calcium, magnesium, or potassium) or an increase in unmeasured anions.

The two most commonly recognized metabolic acidoses in adult patients are an elevated anion gap acidosis secondary to lactate and a normal anion gap acidosis secondary to prolonged diarrhea. The latter marks the most commonly diagnosed cause of acidosis in pediatric patients.

Elevated anion gap acidoses

The elevation of the anion gap is created by inorganic (eg, phosphate, or sulfate), organic (eg, ketoacids or lactate), or exogenous (eg, salicylates) acids incompletely neutralized by bicarbonate. The most common etiologies of elevated anion gap acidoses can be remembered using the mnemonic MUDPILES: methanol, uremia, diabetic and alcoholic ketoacidosis, paraldehyde, isoniazid or iron, lactate, ethylene glycol, and salicylates (Box 1). A subsegment of these elevated anion gap acidoses are referred to as high-anion gap acidoses, which are defined by the coexistence of an

Box 1. Etiologies of elevated anion gap acidosis

Methanol

Uremia

Diabetic, alcoholic, and starvation ketoacidosis

Paraldehyde

Isoniazid and iron

Lactic acidosis

Ethylene glycol

Salicylates

elevated anion gap and a decreased $[\text{HCO}_3^-]$. There are four principle etiologies of high-anion-gap acidosis: lactic acidosis, ketoacidosis, ingested toxins, and renal failure.

Methanol

Methanol is widely available in paints, solvents, antifreeze, and fuel for outdoor stoves and torches; therefore an index of suspicion for exposure plays a large part in diagnosing methanol-induced acidosis. Absorption takes place by means of gastrointestinal (GI), dermal, and respiratory routes [1–3]. Methanol is converted to formaldehyde by alcohol dehydrogenase, then to formic acid (formate). The formic acid accumulates, leading to physiologic effects and anion gap acidosis. Signs and symptoms may be delayed for 30 hours or more following exposure [4]. Methanol's toxicity predominantly affects the neurologic, ophthalmologic, and GI systems. The state of inebriation caused by methanol often has elapsed before presentation with neurologic symptoms (such as headache and dizziness) caused by the formate [4]. Agitation, acute mania, amnesia, decreased level of consciousness, and seizures, however, can complicate the initial presentation [1,5–9]. Ophthalmologic complaints may develop as early as 6 hours postexposure or be delayed greater than 24 hours. In two large case series, all patients with acidemia had ophthalmologic complaints [1,10]. Symptoms include blurred vision, photophobia, visual hallucinations, and varying degrees of visual impairment [1,9,11–13]. Examination findings range from normal to retinal edema associated with unreactive pupils and absent vision [1,9,11–13]. GI effects frequently are limited to nausea and vomiting, but may include severe abdominal pain, GI hemorrhage, diarrhea, liver function abnormalities, and pancreatitis [1,7–9,13].

In addition to an anion gap acidosis, methanol toxicity also results in a difference between the measured serum and calculated serum osmolalities, referred to as an osmolal gap. A normal osmolal gap has been defined as less than 10 mOsm/kg. As baseline osmolal gaps vary among patients, however, methanol toxicity cannot be ruled out by the presence of a normal gap [4]. Methanol levels can be measured to further confirm diagnostic suspicion of methanol toxicity; however, such levels are rarely available in real time and only measure methanol that has not been metabolized. Methanol levels greater than 20 mg/dL or less than 20 mg/dL with an accompanying acidosis are considered toxic [4]. Finally, imaging may reveal cerebral edema or basal ganglia hemorrhages or infarcts in severely ill patients with methanol toxicity [14–18].

Uremia

A history of progressive renal disease and elevated serum urea nitrogen (BUN) and creatinine levels are keys to diagnosing elevated gap acidosis as

a result of chronic renal failure. Normal anion gap metabolic acidosis accompanies renal insufficiency, and progresses to elevated gap acidosis as the glomerular filtration rate (GFR) decreases and renal failure ensues. With a decrease in GFR comes decreasing filtration and increasing reabsorption of inorganic and organic acids, leading to an increased anion gap [19]. Furthermore, a decreasing number of functioning nephrons results in reduced NH_4 production, resulting in an insufficient amount of NH_4 to buffer the net increase in acids [19,20]. Bicarbonate concentration rarely falls below 15 mmol/L, and the anion gap rarely exceeds 20 mmol/L [19].

Physical manifestations of the uremic syndrome involve multiple systems. Neurologically, daytime drowsiness progresses to obtundation, while distal dysesthesias result from uremia's effects on the peripheral neurologic system. Atherosclerosis and noncardiogenic pulmonary edema predominate among cardiovascular effects. GI manifestations include anorexia with subsequent nausea and vomiting, often progressing to gastritis and peptic ulcer disease. Uremic patients commonly complain of diffuse pruritus; both dystrophic calcifications and changes in skin pigmentation may be present also. Anemia and platelet dysfunction result from uremia. Finally, the endocrinologic effects of uremia encompass insulin resistance, hyperlipidemia, hyperparathyroidism, and gonadal atrophy with associated dysfunction [20].

Ketoacidoses: diabetic, alcoholic, and starvation

Diabetic ketoacidosis (DKA) encompasses a triad of clinical findings: hyperglycemia, ketonemia, and acidemia. It occurs most often in people with type I diabetes; however, there are occurrences in people with type II diabetes. The latter occurs predominantly in obese, African-American type II diabetics [21,22]. Onset of DKA requires the shortage or absence of insulin coupled with increased levels of glucagon. Most often this state is caused by noncompliance with an insulin regimen or to a period of increased physical stress (eg, infection or surgery). In the face of insulin noncompliance, glucagon levels increase in response to insulin withdrawal. In the face of physical stress, rising levels of epinephrine are thought to stimulate glucagon release. In both scenarios, glucagon leads to the ketoacidotic state by means of two pathways. By means of the first pathway, glucagon initiates gluconeogenesis and impairs peripheral glucose use, resulting in hyperglycemia followed by an osmotic diuresis. By means of the second pathway, glucagon stimulates hepatic oxidation of free fatty acids released from adipose tissue as a result of insulin deficiency. Oxidation of free fatty acids produces ketoacids, β -hydroxybutyrate, and acetoacetate, leading to metabolic acidosis.

Patients suffering from DKA often present with nausea, vomiting, and polyuria that may be associated with abdominal pain. Exam reveals Kussmaul respirations and signs of dehydration. Without treatment, DKA

may progress, leading to a decreasing level of consciousness and rarely, circulatory collapse. A case series of 308 patients with nonfatal DKA demonstrated the following common laboratory abnormalities:

- A mean serum glucose of 675 mg/dL, a mean serum sodium of 131 mmol/L (caused by increased intracellular water in the plasma space in response to the hyperglycemia-induced osmolality rise)
- A mean serum potassium of 5.3 mmol/L (secondary to the insulin shortage, which traps potassium in the plasma space)
- A mean serum bicarbonate of 6 mmol/L [23,24]

In addition to the hyperglycemic state, the presence of ketonuria, assessed by the nitroprusside reaction with acetoacetate, helps set the diagnosis of DKA apart from most remaining sources of elevated anion gap acidosis. In the presence of mild hyperglycemia, ketonuria, and an insufficient history of present illness, however, serum dilution followed by ketone testing may be required to differentiate DKA from other ketoacidoses. Patients with DKA have a lower β -hydroxybutyrate to acetoacetate ratio, resulting in positive serum ketone testing at dilutions greater than 2:1, setting them apart from patients with alcoholic or starvation ketoacidosis [25].

The diagnosis of alcoholic ketoacidosis (AKA) is accelerated by the frequently difficult to elicit history of chronic alcoholism, most often including a recent binge followed by an abrupt cessation of alcohol use. As in DKA, glucagon levels are elevated because of insufficient intracellular glucose, leading to ketoacid formation. Clinical presentation is remarkable for vomiting, abdominal pain, and dehydration. In contrast to DKA, serum glucose levels are most often low to normal. Furthermore, the rise in the β -hydroxybutyrate to acetoacetate ratio from 3:1 in DKA to 7:1 in (AKA) results in a nitroprusside test that is more often negative because of the relative lack of acetoacetate [19,25].

Starvation ketoacidosis occurs during fasting in the face of physiologic stress, such as illness, exercise, or pregnancy [26–30]. During this time, starvation-induced absence of insulin stimulates the previously discussed ketogenic pathway, accounting for the pathogenesis of acute starvation ketoacidosis [26]. As in AKA, the serum glucose level is low to normal, and serum ketones may not be found if the nitroprusside test is used, because of a predominance of β -hydroxybutyrate.

Paraldehyde

Several decades ago, paraldehyde was used as a pharmacologic treatment for alcohol withdrawal. In overdose, paraldehyde's clinical picture matches that of a sedative–hypnotic overdose: hypotension, bradypnea, hypothermia, and altered mental status [31]. Ingestion leads to formation of acetic and chloracetic acids, which create the elevated anion gap in the resultant metabolic acidosis [32].

Isoniazid and iron

After being on a steady decline for more than 20 years, the incidence of tuberculosis in the United States rose each year after 1985, until peaking in 1992 [33]. As the primary antituberculin agent for prophylaxis and initial single- and multi-drug therapy of tuberculosis, it seems only logical that isoniazid (INH) usage also rose. Isoniazid toxicity may be acute, indirectly-mediated depletion of pyridoxine or a chronic, directly-mediated, hypersensitivity reaction. It is the former that leads to a relative γ -aminobutyric acid (GABA) deficiency, resulting in refractory generalized, tonic-clonic seizures [34]. Anion gap metabolic acidosis is the product of a rapid, excessive accumulation of lactate during these seizures. The lactate cannot be cleared secondary to INH's inhibition of the formation of nicotinamide adenine dinucleotide (NAD), an essential cofactor in the conversion of lactate to pyruvate [34]. In addition, INH decreases the metabolism of β -hydroxybutyrate, further contributing to the elevated anion gap acidosis [35].

Before the onset of seizures and metabolic acidosis, acute INH overdoses may present with vomiting, diaphoresis, tachycardia, and hypertension occurring within 30 minutes of ingestion [36]. Agitation, altered mental status, and hallucinations have been reported, likely secondary to the decrease in GABA [34]. Associated seizures are generalized, classically prolonged, and refractory to standard antiepileptic therapy [34]. Hemodynamic instability may occur in the patient with seizures and acidosis [36,37].

Similar to INH, iron exhibits a direct and indirect toxicity; however, unlike INH, both types occur with acute overdose in a dose-dependent fashion. Iron mediates direct GI toxicity after its absorption into the vascular walls, resulting in GI cell necrosis and hemorrhage [38]. There is also evidence that iron may act as a direct myocardial toxin [39]. Unbound iron, which remains after transferrin is saturated, creates indirect cellular toxicity. It uncouples mitochondrial oxidative phosphorylation, thereby devastating ATP synthesis. It also forms free radicals, which damage cell membranes by means of lipid peroxidation [40,41]. Impaired ATP synthesis has its most damaging effects on GI, cardiovascular, hepatic, and central nervous system (CNS) cells because of their high metabolic activity. This damage furthers the aforementioned GI hemorrhage and myocardial dysfunction and adds hepatic failure and CNS dysfunction to the realm of iron toxicity [42]. The elevated anion gap consists of lactate produced as a result of hypovolemia, cardiogenic shock, and anaerobic metabolism, and of unbuffered protons produced as a result of free ferric iron hydration.

When considering iron overdose as part of a differential diagnosis, it is hoped that history consistent with iron ingestion or an abdominal radiograph revealing radiopaque tablets can be obtained. Without these hints, diagnosis relies on recognition of the clinical stages of iron poisoning and an elevated iron level drawn 3 to 5 hours postingestion in the presence of an elevated anion gap acidosis. Clinically, iron poisoning takes place in

five stages [43]. The elevated anion gap metabolic acidosis is most prominent in stages two through four, corresponding to several hours up to 5 days postingestion. Stage 1 consists of GI symptoms ranging from abdominal pain and vomiting to life-threatening GI hemorrhage. Symptoms begin 1 to 6 hours after an ingestion of greater than 10 to 20 mg/kg of elemental iron and may be delayed with enteric-coated preparations. Stage 2 represents a period of relative stability in which GI symptoms abate; however, subclinical hypoperfusion and metabolic acidosis persist. This stage may last up to 24 hours. Although some patients may recover from stage 2, many who have ingested more than 40 mg/kg progress to the systemic toxicity. The onset of stage 3 occurs 24 to 48 hours postingestion and is characterized by reoccurrence of GI symptoms, hypoperfusion, severe metabolic acidosis, altered mental status, and coagulopathy. Although stage 3 accounts for the highest number of iron poisoning deaths, iron levels are often normal by this stage. Progression to stage 4 is rare; it is marked by acute hepatic failure and encephalopathy. Those who recover from an acute iron overdose, may present subacutely, 2 to 4 weeks postoverdose, in stage 4 with a bowel obstruction caused by GI scarring [42,44].

Lactic acidosis

There are three general categories of lactic acidosis. The L isomer of lactate is most common and what usually is measured when obtaining serum lactate levels. It is also responsible for the first two categories of lactic acidosis referred to as types A and B. These two distinctions refer to those etiologies that produce lactic acidosis by means of tissue hypoxia (type A) and those that are accompanied by normal oxygen delivery (type B). The D isomer is responsible for the third type of lactic acidosis, which occurs in patients with small bowel resection or jejunoileal bypass. The D lactate is formed by colonic bacteria after ingestion of a large carbohydrate load in the face of carbohydrate malabsorption [45]. It cannot be metabolized by lactate dehydrogenase, leading to accumulation that presents clinically with an encephalopathy and elevated anion gap acidosis [46].

Type A lactic acidosis can be the result of hemodynamic shock, severe hypoxemia or anemia, vigorous exercise, mesenteric ischemia, or mitochondrial dysfunction. All types of hemodynamic shock; hypovolemic, septic, cardiogenic, anaphylactic, and spinal shock limit the delivery of oxygen secondary to diminished blood flow to the tissue. It is beyond the scope of this article to discuss the differential diagnosis of shock. Severe hypoxemia caused by such entities as pulmonary disease processes or pulmonary embolism can be identified easily with pulse oximetry or arterial blood gas measurement. Anemia is readily identifiable with the measurement of a hemoglobin or hematocrit. Exercise above the anaerobic threshold, including seizures and hypothermic shivering, results in a relative tissue hypoxia secondary to an unmet increased oxygen demand. Some texts

classify seizures as type B acidoses, presumably because of the increased lactate production [19]. Lactic acidosis may be attributed to anaerobic exercise in patients with the appropriate history or with myoglobinuria and elevated creatinine phosphokinase (CPK). Mesenteric ischemia-induced lactic acidosis most often presents in conjunction with abdominal pain out of proportion to exam in a patient population with risk factors for either a low-flow state or an embolic event. Despite the presence of risk factors, abdominal pain, and elevated gap acidosis, imaging or surgery often is required to confirm the diagnosis. Finally, mitochondrial dysfunction can be the consequence of a congenital enzyme defect or, more commonly, mediated by toxins. Examples of the former include mitochondrial encephalopathy with acidosis and stroke (MELAS) and Pearson syndrome, often diagnosed in childhood after extensive genetic evaluation. Examples of the latter include carbon monoxide, which inhibits delivery of oxygen to the mitochondria by means of the binding of hemoglobin, and cyanide, which directly binds and inactivates complex IV of the mitochondrion's electron transport chain. In both scenarios, mitochondrial dysfunction results in lactic acid production caused by the anaerobic metabolism of pyruvate.

Type B lactic acidoses result from an overproduction or decreased hepatic removal of lactate in the face of maintained oxygen delivery to the tissues. The etiologies of type B acidoses are as follows: hypoglycemia/glycogen storage disease, diabetes mellitus, ethanol, hepatic failure, malignancy, and drugs. In the face of hypoglycemia, epinephrine and glucagon are secreted to stimulate the breakdown of glycogen to glucose. In patients with limited or abnormal glycogen stores, however, the amount of glucose generated is not sufficient, and glycolysis ensues, leading to increased pyruvate and lactate. In diabetic patients, low insulin levels reduce the activity of pyruvate dehydrogenase, resulting in increased lactate levels. In addition, there is evidence that the existence of plasma ketones inhibit hepatic uptake of lactate [47]. In the intoxicated patient, ethanol increases the NADH/NAD ratio, favoring the conversion of pyruvate to lactate, instead of glucose. Hepatic failure results in lactic acidosis caused by the liver's failure to remove lactate, either by converting it to carbon dioxide and water or to glucose. Lactic acidosis has been described in cancer patients in the absence of tissue hypoperfusion and other known causes of increased lactate production. Known as lactic acidosis of malignancy, it has been reported in patients with Hodgkin's disease, acute leukemia, and sarcoma [48–50]. Although many common medications are known to cause hyperlactatemia, some of the most pronounced elevated lactate levels are seen in those patients taking biguanides and nucleoside analog reverse transcriptase inhibitors (NRTIs) or those on propofol infusions. Severe, life-threatening lactic acidosis has been associated with biguanides, such as metformin, in two clinical settings: renal insufficiency and overdose [51]. It appears as though prescribed use in uncomplicated noninsulin-dependent diabetes mellitus patients does not pose a risk for severe acidosis. The

occurrence of mildly symptomatic to severe lactic acidosis in HIV patients under treatment with NRTI therapy is thought to be caused by mitochondrial disruption; however, it thus far has not been associated with specific clinical scenarios. A recent case review reported female sex to be an independent risk factor for development of lactic acidosis and suggested that duration of NRTI therapy, specific drug use, and genetic predisposition also may be risk factors [52]. Finally, deaths have been reported in children and adults undergoing propofol infusions of greater than 48 hours. Propofol infusion syndrome includes cardiac failure, rhabdomyolysis, severe metabolic acidosis, and renal failure. The metabolic acidosis is thought to be the result of impaired free fatty acid use and mitochondrial activity [53].

Ethylene glycol

Ethylene glycol lowers the freezing point of water, and is therefore most often found in antifreeze, deicing solutions, and brake fluid. As with methanol, a high index of suspicion for exposure plays a large part in the diagnosis of poisoning. Absorption takes place in the GI tract; skin and inhalational exposures are negligible [4]. Ethylene glycol is converted to glycoaldehyde by alcohol dehydrogenase, then to glycolic acid, glyoxylic acid, and oxalic acid [54]. The elevated anion gap acidosis primarily is caused by the accumulation of glycolic acid with minimal assistance from lactic acid [55–57]. Until recently, however, ethylene glycol's toxic effects have been attributed solely to calcium oxalate crystal deposition. Although suggested in the 1970s, the direct toxic effect of ethylene glycol's organic acid metabolites was not demonstrated until recently [58,59]. Signs and symptoms typically occur within 4 to 8 hours of ingestion, but may be prolonged for 12 or more hours if ingested with ethanol [4]. Ethylene glycol's toxicity reveals itself clinically in four stages, with predominant effects on the neurologic, cardiopulmonary, and renal systems. Stage 1 is referred to as the acute neurologic stage in which ethylene glycol results in an inebriated state similar to that of ethanol. Larger ingestions may result in hallucinations, seizures, or coma. Stage 2, the cardiopulmonary stage, begins 12 to 24 hours postingestion and is characterized by hypertension, tachycardia, and tachypnea. Although the tachypnea may occur solely in response to metabolic acidosis, it also may be the harbinger of ensuing pulmonary edema secondary to myocardial depression or direct pulmonary toxicity. In addition, hypocalcemia, secondary to the chelation of calcium by oxalic acid, and myositis, heralded by CPK elevations, may be present. Stage 3, the renal stage, occurs 24 to 72 hours postingestion and is distinguished by flank pain and acute tubular necrosis (ATN) with or without oliguria. Increased degree of acidosis, delay in presentation, and glycolic acid levels predict progression to renal failure more reliably than ethylene glycol levels [59–61]. Stage 4, the delayed neurologic sequelae stage, presents with cranial nerve palsies approximately 1 week after ingestion.

Similar to methanol toxicity, ethylene glycol toxicity classically results in elevated anion and osmolal gaps but cannot be ruled out by the presence of a normal osmolal gap [54]. Additionally, levels greater than 20 mg/dL or less than 20 mg/dL with an accompanying acidosis are considered toxic. Unlike methanol, there are many laboratory-based clues that can further the clinician's diagnostic suspicion of ethylene glycol ingestion [4]. Approximately half of ethylene glycol intoxicated patients exhibit envelope-shaped calcium oxalate dihydrate or needle-shaped calcium oxalate monohydrate crystalluria [55,62]. Both freshly voided urine and fresh emesis with pH greater than 4.5 will fluoresce under a Wood's lamp if fluorescein-containing antifreeze has been ingested [4]. An EKG may demonstrate a prolonged QT interval, providing a clue to ethylene glycol-induced hypocalcemia. Finally, cerebral imaging studies show cerebral edema with decreased attenuation in the basal ganglia, thalami, midbrain, and upper pons [63,64].

Salicylates

Acute and chronic toxicity can result from ingestion of salicylates found in oral medications, either alone or in combination with decongestants, antihistamines, or opioids, and from some skin and teething ointments, sunscreens, and antidiarrheals that contain salicylate compounds. Salicylates create a mixed acid–base disturbance by means of direct stimulation of the medullary respiratory center, leading to respiratory alkalosis, and uncoupling of oxidative phosphorylation, leading to metabolic acidosis. The metabolic acidosis then is amplified by renal bicarbonate excretion in response to increased ventilation, lactic acid accumulation resulting from mitochondrial impairment, ketoacid production caused by salicylate-induced inhibition of Krebs cycle dehydrogenases, and free salicylic acid [65]. Serum salicylate levels peak 2 to 4 hours after an acute ingestion. A level of 30 mg/dL following an acute ingestion is potentially toxic, whereas chronic toxicity may occur even at a therapeutic level of 4 to 6 gm/dL. Clinically, an elevated salicylic acid concentration appears as tachypnea or hyperpnea, caused by direct medullary stimulation, and hyperthermia, caused by the uncoupling of oxidative phosphorylation. Vasoconstriction of the auditory microvasculature generates tinnitus during the initial presentation of toxicity. Vomiting begins 3 to 8 hours postingestion as a result of direct stimulation of the medullary chemoreceptors. Severe dehydration may ensue as a consequence of increased ventilation, vomiting, and hyperthermia. CNS manifestations parallel increasing acidemia, as an increased amount of nonionized salicylic acid results in increased intracellular levels. Increased capillary permeability in the pulmonary and cerebral tissue may result in edema; the mechanism is thought to relate to salicylate's blockade of the cyclooxygenase pathway leading to production of proinflammatory leukotrienes. Rarely, mucosal bleeding results from

salicylate's platelet inhibition and depression of hepatic synthesis of factor VII.

The presentation of salicylism, characterized by hyperthermia, altered level of consciousness, pulmonary edema, and shock in the face of a mixed acid–base disorder may present a diagnostic dilemma or even point directly toward a septic etiology without the available history implicating an acute or chronic salicylate overdose. Although tinnitus may point the clinician in the correct direction early in the course of toxicity, this history is often unavailable. Thus a high index of suspicion must be maintained in the face of an anion gap acidosis. The urine ferric chloride test provides a timely and simple way to check for the presence of salicylates at the bedside. It is performed by placing a few drops of 10% ferric chloride solution in a patient's urine, which will indicate the presence of salicylates by turning purple immediately [66]. Although it does not give a quantitative result and cannot confirm toxicity, a negative result indicates that the metabolic disturbances are unlikely the result of salicylates. An elevated serum salicylate level is required to confirm toxicity in the case of an acute overdose, while persistent symptoms and associated laboratory abnormalities may indicate the presence of chronic overdose in the face of mildly elevated serum salicylate levels.

Hyperchloremic or normal anion gap acidoses

The presence of a hyperchloremic or normal anion gap acidosis occurs by means of an excessive loss of HCO_3^- or an inability to excrete H^+ . HCO_3^- can be lost from the GI tract or from the kidneys, whereas, the inability to excrete H^+ is a result of renal failure. More recent literature advocates calculation of a urinary anion gap (UAG) to aid in differentiating etiologies of an existing hyperchloremic acidosis. Although a negative UAG suggests GI HCO_3^- loss, a positive UAG indicates inability to excrete H^+ [67]. In hyperchloremic acidosis, the increase in $[\text{Cl}^-]$ equals the decrease in $[\text{HCO}_3^-]$. Conditions in which this relationship does not exist must be classified as mixed acid–base disorders. The etiologies of a hyperchloremic or normal anion gap acidosis can be remembered by the mnemonic HARD UP: hyperalimentation, acetazolamide, renal tubular acidoses and renal insufficiency, diarrhea and diuretics, ureterostomy, and pancreatic fistula (Box 2). Diarrheal and renal etiologies are by far the most common.

Hyperalimentation

Hyperchloremic acidosis results from parenteral hyperalimentation administered without a sufficient amount of bicarbonate or bicarbonate-yielding solutes, such as lactate or acetate [68]. Protons are released from synthetic, positively charged amino acids (eg, arginine, lysine, or histidine)

Box 2. Etiologies of normal anion gap acidosis

Hyperalimentation

Acetazolamide (carbonic anhydrase inhibitors)

Renal tubular acidosis and renal insufficiency

Diarrhea and diuretics

Ureteroenterostomy

Pancreatic fistula

in hyperalimentation mixtures as they are metabolized. In the face of a relative bicarbonate deficiency, these protons cannot be buffered, leading to a normal anion gap acidosis.

Acetazolamide (and carbonic anhydrase inhibitors)

Acetazolamide may be used in the treatment of high altitude sickness, glaucoma, hyperuricemia, and hypokalemic periodic paralysis. It therefore should be suspected as an etiology of normal gap metabolic acidosis in patients with history of such illnesses and laboratory findings remarkable for an increased $[\text{Cl}^-]$ and decreased $[\text{HCO}_3^-]$. Acetazolamide and other carbonic anhydrase inhibitors work as proximal tubule diuretics by blocking the catalytic dehydration of luminal carbonic acid. This blockade prevents the proximal reabsorption of sodium bicarbonate. Acetazolamide's blockade of HCO_3^- reabsorption does not cause a severe metabolic acidosis because of HCO_3^- reabsorption at more distal nephron sites and decreased filtration of HCO_3^- in the presence of metabolic acidosis [69].

Renal tubular acidoses and renal insufficiency

Type 1 renal tubular acidosis (RTA), or distal RTA, most often occurs as a secondary distal RTA in association with a systemic inflammatory illness such as Sjögren's syndrome or multiple myeloma. Rarely, it can be an inherited disorder, a result of chronic renal transplant rejection, or drug-induced [19]. Type 1 RTA is a consequence of the failure of one or both of the collecting duct proton pumps (H^+ -ATPase and H^+ K-ATPase) to excrete H^+ . The failure of these pumps results in the inability to acidify the urine below a pH of 5.5. The elevated urinary pH does not allow adequate trapping of NH_4 in the collecting duct. Hence, the clinical findings of a type 1 or distal RTA include: hypokalemia, hyperchloremic acidosis, low urinary NH_4 , and urine pH greater than 5.5. Chronic toluene abuse and lithium, pentamidine, and rifampin use produce a type 1 RTA with similar findings [19,69,70]. Amphotericin B use produces a picture clinically consistent with

type 1 RTA by means of an alteration in distal nephron permeability that allows leakage of H^+ from lumen to blood, thereby destroying the pH gradient and reducing net H^+ secretion [71].

Type 2 RTA, or proximal RTA, also is referred to as Fanconi syndrome. Proximal RTA is found most commonly in children. In adults, it usually is associated with multiple myelomas, in which increased excretion of immunoglobulin light chains injures the proximal tubule epithelium, or use of carbonic anhydrase inhibitors. Physiologically, generalized proximal tubular dysfunction leads to bicarbonaturia until steady state is reached, and persistent proteinuria, glycosuria, aminoaciduria, and phosphaturia. Unlike type 1 RTA, urinary pH is appropriately acidic because of a steady state in which the amount of $[HCO_3^-]$ filtered does not exceed that which can be reabsorbed distally. Enhanced Cl^- reabsorption, stimulated by volume contraction, results in hyperchloremia. In untreated patients, serum $[HCO_3^-]$ is low, reaching a nadir of 15 to 18 mEq/L. The rate of K excretion is proportional to the HCO_3^- delivery to the distal nephron, leading to an associated hypokalemia.

The diagnosis of type 2 RTA relies on the recognition of a chronic hyperchloremic metabolic acidosis accompanied by acidic urine, hypokalemia, and a low fractional excretion of HCO_3^- . With infusion of sodium bicarbonate, bicarbonaturia ensues, and the urine becomes alkaline. A further diagnostic clue is the large amounts of exogenous HCO_3^- required to correct plasma $[HCO_3^-]$.

Hyperchloremic metabolic acidosis occurs in 50% of patients with hyporeninemic hypoaldosteronism, also known as type 4 RTA [69]. This syndrome occurs in older patients with interstitial renal disease, hypertension, diabetes mellitus, and concurrent congestive heart failure [68,69]. Distal tubular damage produces diminished rates of Na absorption, H^+ secretion, and K secretion. A clinical triad of hyponatremia, hyperkalemia, and hyperchloremic acidosis is the hallmark of this disorder. Diuretics such as triamterene, spironolactone, and amiloride create a similar syndrome [68].

As discussed previously, renal failure results in an elevated anion gap uremic acidosis, secondary to decreased filtration of acids and decreased ammoniogenesis. Early in renal disease, however, when the GFR is between 20 and 50 mL per minute, a hyperchloremic acidosis is present because of the decreased ability of the kidneys to compensate with adequate HCO_3^- reabsorption.

Diarrhea and diuretics

The most common normal anion gap acidosis results from the GI HCO_3^- loss that accompanies diarrhea. Stool contains large amounts of HCO_3^- in addition to the organic ions that are absorbed and converted to HCO_3^- ; both are lost with diarrhea. Stool contains a greater amount of sodium relative to chloride, resulting in a diarrhea-induced relative hyperchloremia.

Hypokalemia exists in large part because of the large quantities of K lost from stool, but also from a hypovolemia-induced hyper-renin-hyper-aldosterone state that enhances renal K secretion. Although acidic urine production would be anticipated in the face of such a metabolic acidosis, urine produced in conjunction with diarrheal illness more often has a pH of 6.0 or higher [72]. Increased urine pH occurs in the face of metabolic acidosis and hypokalemia because of increased renal NH_4 synthesis and excretion. With a concurrent history of diarrhea, it is this fact that allows hyperchloremic metabolic acidosis of GI origin to be differentiated from that of RTA.

As mentioned previously, diuretics such as triamterene, spironolactone, and amiloride interfere with distal tubular Na absorption, H^+ secretion, and K secretion, resulting in a hyperkalemic, hyperchloremic metabolic acidosis resembling that of type 4 RTA [68].

Ureteroenterostomy and enterostomy

Although now rare, ureteroenterostomy (surgical insertion of the ureters into the bowel) was the first form of diversion to be popularized for patients with exstrophy. This style of diversion results in hyperchloremic metabolic acidosis, because the urine reaching the colon is alkalinized by colonic bicarbonate secretion in exchange for chloride [68]. Other types of enterostomies, tube drainage, and fistulae that result in loss of HCO_3^- rich intestinal and biliary fluid also result in normal gap metabolic acidosis.

Pancreatic fistula

External pancreatic fistulas occur as a consequence of surgical therapy for chronic pancreatitis or pseudocyst, whereas internal fistulas occur mainly in the setting of chronic pancreatitis after rupture of a pseudocyst [73]. The fluid from an internal fistula may track to the peritoneal cavity or pleural space, a diagnosis that can be established by documenting high levels of amylase within the respective fluid. In either scenario, HCO_3^- rich pancreatic fluid is diverted from the bowel where normal HCO_3^- reabsorption occurs. This loss of HCO_3^- results in a normal gap metabolic acidosis.

Summary

Although the presence and etiology of a metabolic acidosis in a tachypnic, dehydrated patient with a sweet odor on his or her breath and complaints of vomiting and polyuria is obvious, the physician is rarely so fortunate. More often, a metabolic acidosis must be confirmed by means of a simultaneous arterial blood gas and an electrolyte panel. Serum anion gap must be calculated to differentiate between an elevated gap and normal gap acidosis.

The applicable mnemonic must be recalled, and each etiology examined and considered or rejected as a possibility in the given clinical scenario. As in nearly every etiology discussed in this article, the key to diagnosis can be found with a careful history and a high index of suspicion for toxic exposure.

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